CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 021028

PRINTED LABELING

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DRAFT PACKAGE INSERT

Information for the patient who uses

Velosulin® BR
Buffered Regular
Human Insulin Injection (rDNA origin)

100 units/mL

FOR USE IN EXTERNAL INSULIN INFUSION PUMPS OR WITH U-100 INSULIN SYRINGES

Please read this leaflet carefully.

WARNINGS

ANY CHANGE OF INSULIN SHOULD BE MADE CAUTIOUSLY AND ONLY UNDER MEDICAL SUPERVISION. CHANGES IN PURITY, STRENGTH (E.G., U-40, U-100), MANUFACTURER, TYPE (E.G., LENTE® NPH, REGULAR) OR SPECIES (BEEF, PORK, BEEF/PORK, HUMAN) MAY RESULT IN THE NEED FOR A CHANGE IN DOSAGE. ADJUSTMENT MAY BE NEEDED WITH THE FIRST DOSE OR OVER A PERIOD OF SEVERAL WEEKS. BE AWARE THAT SYMPTOMS OF HYPOGLYCEMIA (LOW BLOOD GLUCOSE) OR HYPERGLYCEMIA (HIGH BLOOD GLUCOSE) MAY INDICATE THE NEED FOR DOSAGE ADJUSTMENT. PLEASE READ SECTIONS ENTITLED "INSULIN REACTION" AND "DIABETIC KETOACIDOSIS AND COMA".
VELOSULIN® BR SHOULD NOT BE MIXED WITH ANY OTHER INSULIN SINCE THE BUFFERING AGENT IN VELOSULIN® BR MAY INTERACT WITH THE OTHER INSULIN AND RESULT IN A CHANGE OF ACTIVITY.
CHANGE THE CATHETER TUBING, THE INSULIN, AND THE RESERVOIR EVERY 48 HOURS.

INSULIN USE IN DIABETES

Your physician has explained that you have diabetes and that your treatment involves the use of insulin or insulin therapy combined with an oral antidiabetic medicine. Insulin is normally produced by

the pancreas, a gland that lies behind the stomach. Without insulin, glucose (a simple sugar made from digested food) is trapped in the bloodstream and cannot enter the cells of the body. Some patients who do not make any or enough of their own insulin, or who cannot use the insulin they do make properly, must take insulin by injection in order to control their blood glucose levels.

Each case of diabetes is different and requires direct and continued medical supervision. Your physician has told you the type, strength and amount of insulin you should use and the time(s) at which you should administer it, and has also discussed with you a diet and exercise schedule. You should contact your physician if you experience any difficulties or if you have any questions.

TYPES OF INSULINS

Standard and purified animal insulins as well as human insulins are available. Standard and purified insulins differ in their degree of purification and content of noninsulin material. Standard and purified insulins also vary in species source; they may be of beef, pork, or mixed beef and pork origin. Human insulin is identical in structure to the insulin produced by the human pancreas, and thus differs from animal insulins. Insulins vary in time of action and in strength; see PRODUCT DESCRIPTION for additional information. Your physician has prescribed the insulin that is right for you; be sure you have purchased the correct insulin and check it carefully before you use it.

PRODUCT DESCRIPTION

Velosulin® BR is a clear solution of insulin in a phosphate buffer. The concentration of this product is 100 units of insulin per milliliter. This human insulin is structurally identical to the insulin produced by the pancreas in the human body. This structural identity is obtained by recombinant-DNA technology utilizing Saccharomyces cerevisiae (bakers' yeast) as the production organism. When a U-100 insulin syringe is used to deliver the insulin, the effect of Velosulin® BR begins approximately ½ hour after the injection. The effect lasts up to approximately 8 hours with a maximal effect between the 1st and 3rd hour.

The time course of action of any insulin may vary considerably in different individuals, or at different times in the same individual, or when using an external insulin infusion pump to deliver the insulin. Because of this variation, the time periods listed here should be considered as general guidelines only when using U-100 insulin syringes to deliver the insulin.

STORAGE

Insulin should be stored in a cool place, preferably in a refrigerator, but not in the freezing compartment. **Do not use insulin if it has been frozen.** Keep the insulin in its carton so that it will stay clean and protected from light. If refrigeration is not possible, the bottle of insulin which you are currently using can be kept unrefrigerated as long as it is kept as cool as possible (below 86°F [30°C]) and away from heat and sunlight. Never use Velosulin® BR if it becomes viscous (thickened) or cloudy. Use it only if it is clear and colorless.

Never use insulin after the expiration date which is printed on the vial label and carton. Once the vial has been opened, it should be used within four weeks (28 days).
(Note: Remove the tamper-resistant cap at first use. If the cap has already been removed, do not use this product and return it to your pharmacy.)

EXTERNAL INSULIN INFUSION PUMPS

Velosulin®BR is indicated for use with external insulin infusion pumps. Novo Nordisk has demonstrated Velosulin® BR to be compatible with MiniMed® Model 506 external insulin infusion pump, using MiniMed® catheters of Polyfin$_{TM}$ and Sofset$_{TM}$ types without Quick Release. MiniMed® Models 506, 505, and 507 external insulin infusion pumps are equivalent with regard to insulin compatibility. If you have any questions on how to operate the pump, consult with your physician or diabetes educator. **It is important that you follow the instructions in your pump manual.** Failure to follow the instructions may result in an inaccurate insulin dose. The pump manual will also help you in the selection, use and sterilization of the appropriate accessories specific to your pump model. Use the correct reservoir and catheter for the pump that you are using to minimize catheter blockage.
Follow your external insulin infusion pump instructions for filling a new reservoir making certain that there are no large air bubbles in the syringe or the catheter. Before inserting the needle, use soap and water to clean your hands and the skin of the infusion site to avoid infection. Choose a new site for each new needle.
Follow your instructions from your physician or diabetes educator regarding basal infusion rates and mealtime insulin bolus dosages. An insulin bolus should be followed by a meal within 30 minutes. Velosulin® BR is for infusion under the skin. It should not be mixed with any other insulin. To get the most benefit from insulin

infusion, measure your blood sugar levels regularly. This will also help in detecting any possible malfunction of your insulin pump.

Change the catheter tubing, the insulin, and the reservoir every 48 hours.

NOTE: In case of pump interruption or failure, switch back to conventional insulin therapy using U-100 syringes and consult with your physician or diabetes educator. Please see the following information:

INSTRUCTIONS FOR INJECTION USING U-100 SYRINGES

A. PREPARING THE INJECTION

1. Clean your hands and the injection site with soap and water or with alcohol. Wipe the rubber stopper with an alcohol swab.
2. Pull back the plunger of the syringe until the rubber tip reaches the marking for the number of units you will inject.
3. Push the needle of the syringe through the rubber stopper into the vial.
4. Push the plunger all the way in. This inserts air into the vial.
5. Turn the vial and syringe upside down and slowly pull the plunger back to a few units beyond the correct dose.
6. If there are air bubbles, flick the syringe firmly with your finger to raise the air bubbles to the needle, then slowly push the plunger to the correct unit marking.
7. Remove the needle from the vial.

B. GIVING THE INJECTION

1. The following areas are suitable for subcutaneous insulin injection: thighs, upper arms, buttocks, or abdomen. Do not change areas without consulting your physician. The actual point of injection should be changed with each injection. Injection sites should be about an inch apart.
2. The injection site should be clean and dry. Pinch up skin area to be injected and hold it firmly.
3. Hold the syringe like a pencil and push the needle quickly and firmly into the pinched-up area.
4. Release the skin and push plunger all the way in to inject insulin beneath the skin. **To ensure that all the insulin is injected, keep the needle in the skin for several seconds after the injection with your finger on the plunger.** Do not inject into a muscle unless your physician has advised it. You should never inject insulin into a vein.

5. Remove the needle. If slight bleeding occurs, press lightly with a dry cotton swab for a few seconds - **do not rub**.

IMPORTANT

Failure to comply with the above instructions and the antiseptic measures may lead to infections at the injection site.
Note: You should use the injection technique recommended by your physician.

USAGE IN PREGNANCY

It is particularly important to maintain good control of your diabetes during pregnancy and special attention must be paid to your diet, exercise and insulin regimens. If you are pregnant or nursing a baby, consult your physician or diabetes educator.

INSULIN REACTION

Insulin reaction (too little sugar in the blood, also called hypoglycemia) can occur if the external infusion pump delivers too much insulin, if you take too large an insulin bolus, skip meals, exercise or work harder than normal. **Hypoglycemia can also happen if you combine insulin therapy and other medications that lower blood glucose, such as oral antidiabetic agents or other prescription and over-the-counter drugs**. The symptoms, which usually come on suddenly, are hunger, dizziness, and sweating. Personality change or confusion may also occur. If you drink or eat something right away (a glass of milk or orange juice, or several sugar candies), you can often stop the progression of symptoms. If symptoms persist, call a physician; an insulin reaction can lead to unconsciousness. If a reaction results in loss of consciousness, emergency medical care should be obtained immediately. If you have had repeated reactions or if an insulin reaction has led to a loss of consciousness, contact your physician. Severe hypoglycemia can result in temporary or permanent impairment of brain function and death.
In certain cases, the nature and intensity of the warning symptoms of hypoglycemia may change. A few patients have reported that after being transferred to human insulin, the early warning symptoms of hypoglycemia were less pronounced than they had been with animal-source insulin.

DIABETIC KETOACIDOSIS AND COMA

Diabetic ketoacidosis may develop if your body has too little insulin. The most common causes are acute illness, infection, failure to take enough insulin by injection, or catheter clogging when used with an

external insulin infusion pump. If you are ill, you should check your urine for ketones. The symptoms of diabetic ketoacidosis usually come on gradually, over a period of hours or days, and include a drowsy feeling, flushed face, thirst, and loss of appetite. Notify a physician immediately if the urine test is positive for ketones (acetone) of if you have any of these symptoms. More severe symptoms are fast, heavy breathing and rapid pulse; if these symptoms occur, you should seek medical attention right away. Severe, sustained hyperglycemia may result in diabetic coma and death.

ADVERSE REACTIONS

Insulin allergy occurs very rarely, but when it does, it may cause a serious reaction including a general skin rash over the body, shortness of breath, fast pulse, sweating and a drop in blood pressure. If any of these symptoms develop you should seek emergency medical care. The formation of fatty lumps at the infusion site or injection site is usually a sign of frequent needle insertion at the same site. Remember to choose new infusion sites or injection sites at which to insert each new needle and consult with your physician or diabetes educator if you develop these fatty lumps at the infusion site. The skin at the infusion site or injection site may also become red, swollen and itchy. This is a local reaction. It may occur if needle insertion is not properly made at the infusion site or injection site, or as a result of skin sensitivity to the cleansing solutions or if the patient is allergic to insulin. If you have a local reaction, consult with your physician or diabetes educator.
Patients with severe systemic allergic reactions to insulin (i.e. generalized urticaria, angioedema, anaphylaxis) should be skin tested with each new preparation to be used prior to initiation of therapy with that preparation.

IMPORTANT NOTES

1. A change in the type, strength, species or purity of insulin could require a dosage adjustment. Any change in insulin should be made under medical supervision.
2. You may have learned how to test your urine or your blood for glucose. It is important to do these tests regularly. Monitor your results and make appropriate dosage adjustments. Contact your physician or diabetes educator for assistance.
3. If you have an illness, especially with vomiting or fever, continue taking your insulin. If possible, stay on your regular diet. If you have trouble eating, drink fruit juices, regular soft drinks, or clear soups; if you can, eat small amounts of bland

foods. Test your urine for glucose and ketones and, if possible, test your blood glucose. Note the results and adjust dosage accordingly or contact your physician or diabetes educator for assistance. If you have severe and prolonged vomiting, seek immediate emergency medical care.

4. You should always carry identification which states that you have diabetes.
5. **Always consult with your physician or pharmacist before taking any new medication.**

Contact your physician if you have any questions about your condition or the use of insulin.

Helpful information for people with diabetes is published by American Diabetes Association, 1160 Duke St., Alexandria, VA 22314.

For information contact: Novo Nordisk Pharmaceuticals, Inc.
Princeton, NJ 08540

Manufactured by: Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark

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APPLICATION NUMBER: 021028

MEDICAL REVIEW(S)

Velosulin is buffered human insulin which is administered by continuous infusion from pumps. This NDA is for a product of recombinant DNA origin. Approvability is to be based on demonstration of bioequivalence and clinical equivalence to the existing semisynthetic product. The Sponsor has submitted two studies, a pharmacokinetic study in normal volunteers and a clinical study in patients with type 1 diabetes mellitus.

Pharmacokinetic study USA 008

24 normal volunteers ages 19-40 were treated in random cross-over fashion with 0.1 units/kg insulin given subcutaneously. One week separated the two treatments. Insulin blood levels, C peptide and glucose were measured for 720 minutes after injection. Results for the major pharmacokinetic parameters are shown below in the table provided by the Sponsor. Based on C max and AUC it is clear that the two products are bioequivalent by standard criteria. In addition, the mean C max for both products is identical at 90.63 minutes . Median values are range are also similar.

RESULTS FOR INSULIN PHARMACOKINETIC PARAMETERS

Parameter	rDNA n = 24	semi synthetic n = 24	Ratio (90% CI)	p-value
Primary Variables				
$AUC_{insulin}$ (min·uU/mL)				
Mean (SD)	12058.88 (2253.59)	12529.72 (3120.16)	0.974	0.268
Median	11286.38	11568.75	(0.94, 1.01)	
Range	8130.75 - 16881.00	8108.25 - 19509.00		
$C_{max\ (insulin)}$ (uU/mL)				
Mean (SD)	44.00 (13.99)	46.27 (12.11)	0.941	0.191
Median	42.35	47.45	(0.87, 1.02)	
Range	26.10 - 90.70	28.40 - 83.60		
Secondary Variables				
$C_{min\ (insulin)}$ (uU/mL)				
Mean (SD)	6.95 (2.46)	6.77 (2.39)	1.019	0.624
Median	6.50	6.05	(0.95, 1.09)	
Range	3.00 - 12.40	3.50 - 13.80		
$T_{max\ (insulin)}$ (min)				
Mean (SD)	90.63 (36.34)	90.63 (63.25)	0.000[a]	0.519
Median	90.00	75.00		
Range	30.00 - 150.00	30.00 - 360.00		
$T_{min\ (insulin)}$ (min)				
Mean (SD)	625.00 (90.07)	582.50 (103.89)	60.00[a]	0.173
Median	660.00	600.00		
Range	360.00 - 720.00	360.00 - 720.00		

a - Difference for T_{max} and T_{min}. P-values and 90% CI for between group comparison in AUC, C_{max}, C_{min} were calculated from ANOVA based on the crossover model, using log-transformed data. For secondary variables, T_{max} and T_{min} the differences between test and reference groups were estimated as the median of the difference within each subject, using raw data, the p-values were calculated using Signed Rank test.

Major Pharmacodynamic parameters are shown in the table below. Mean Blood glucose nadir was about 56 mg/dl after both treatments and the nadir occurred at 135-151 minutes. The nadir of C peptide level was 221-227 minutes. The differences between treatments were small and not statistically significant.

PHARMACODYNAMIC PARAMETERS FOR GLUCOSE PROFILE

Parameter	rDNA n = 24	semi synthetic n = 24	Ratio / Difference (90% CI)	p-value
$AUC_{0\text{-}720}$ (min ·mg/dL)				
Mean (SD)	54788.13 (3688.18)	55324.69 (4894.73)	0.992	0.471
Median	54626.25	54851.25	(0.97, 1.01)	
Range	46680.00 - 63420.00	45945.00 - 67755.00		
C_{min} (mg/dL)				
Mean (SD)	56.04 (9.30)	56.58 (9.68)	0.992	0.805
Median	57.00	59.00	(0.94, 1.04)	
Range	38.00 - 73.00	33.00 - 76.00		
T_{min} (min)				
Mean (SD)	151.25 (91.39)	135.00 (81.56)	0.000	0.358
Median	112.50	105.00	(NA)	
Range	60.00 - 360.00	45.00 - 360.00		

Conclusion

Velosulin R Buffered Human Insulin Semi Synthetic Origin 100 u/mL and Velosulin R Buffered Human Insulin Recombinant DNA Origin 100 u/mL were found to be bioequivalent.

PHARMACODYNAMIC PARAMETERS FOR C-PEPTIDE PROFILE

	rDNA n = 24	semi synthetic n = 24	Ratio / Difference (90% CI)	p-value
$AUC_{0\text{-}720}$ (min ·ng/mL)				
Mean (SD)	536.39 (130.60)	556.08 (165.30)	0.977	0.566
Median	532.43	511.09	(0.91, 1.05)	
Range	351.75 - 792.00	343.35 - 943.13		
C_{min} (ng/mL)				
Mean (SD)	0.38 (0.18)	0.41 (0.18)	0.898	0.382
Median	0.34	0.37	(0.73, 1.10)	
Range	0.13 - 0.80	0.13 - 0.90		
T_{min} (min)				
Mean (SD)	226.88 (66.69)	220.63 (77.94)	0.000	0.566
Median	210.00	210.00	(NA)	
Range	105.00 - 360.00	105.00 - 420.00		

One patient withdrew because of hypoglycemia in the semisynthetic arm. While receiving rDNA insulin, one patient reported a headache and one reported dizziness. After receiving semisynthetic insulin, one patient complained of conjunctivitis, one of keratitis, and two of abdominal pain. All these adverse events were described as mild to moderate.

Clinical Study USA 009

This was a cross-over study in patients with type 1 diabetes experienced in using insulin by subcutaneous infusion. They are instructed to use the new insulin preparation in a manner similar to the preparations they have been accustomed to use before entering the study. Patients are given one insulin preparation for four weeks and are then crossed over to the second insulin preparation. The first week of the four week treatment period is considered "equilibrium". Efficacy data is collected at the end of the second week and for two additional weeks. The primary efficacy variable is the average daily dose of insulin measured for the last three weeks of the four week period. Secondary variables are fructosamine levels at the end of each of the three week periods, three pre-meal and bedtime glucose levels(by home monitoring on fingerstick blood) , number of glucose values over 400 or less than 60 mg/dl and number of obstructions/leakage of infusion.

The study group consisted of 20 patients with type 1 diabetes whose demographic characteristics are shown below(table 6.1). All patients were white, mean age about 36 years , with a range of HbA1c of 5.8-8.9%. Baselin fructosamine values were 259-450 umole/L Patients who received rDNA insulin first had slightly better glycemic control at baseline than patients who received semisynthetic insulin first.

Table 6-1: Summary of Patient's Characteristics

	semi synthetic → rDNA	rDNA → semi synthetic
No. Treated	10	10
Age (yrs)		
Mean (SD)	35.3 (9.60)	37.3 (11.61)
Min - Max	24 - 55	25 - 52
Race (%)		
Caucasian	100.0	100.0
Weight (kg)		
Mean (SD)	82.5 (9.38)	87.8 (9.24)
Min - Max	72 - 103	75 - 102
Height (cm)		
Mean (SD)	176.1 (5.91)	178.6 (7.31)
Min - Max	169 - 186	168 - 191
BMI (kg/m^2)		
Mean (SD)	26.6 (2.39)	27.5 (1.26)
Min - Max	23 - 30	26 - 30
Fructosamine (μmol/L)		
Mean (SD)	331.0 (35.90)	373.5 (37.65)
Min - Max	259 - 365	333 - 450
Hemoglobin A_{1c} (%)		
Mean (SD)	7.4 (0.71)	7.9 (0.75)
Min - Max	5.8 - 8.2	6.7 - 8.9

Data from End-of-Text Table 1

Medical History

As shown below (table 8.1) there was no change in the daily insulin dose between the two therapies.

	rDNA	semi synthetic	
No. Treated	20	20	Between Treatment Comparison
Daily Insulin Dose (unit/kg)			
Mean (SD)	0.576 (0.145)	0.563 (0.156)	Difference = -0.014
Min - Max	0.366 - 0.935	0.306 - 0.911	95% Confidence Interval (-0.042, 0.014)
			p-value = 0.306*

*p value is ANOVA based on the 2x2 crossover model.
Data from End-of-Text Table 6

There was no significant difference in mean daily insulin dosage between rDNA and semi synthetic insulin therapies when treating patients diagnosed with type I diabetes mellitus.

The mean dose for rDNA was 0.576 U/kg compared to 0.563 U/kg for semisynthetic. In both cases, approximately 40%-50% of the insulin was administered as basal infusion (range 21-77%) and percent given as basal infusion compared to premeal bolus was remarkable constant between patients (table 7.1)

Table 7-1: Average Daily Insulin Dose Over 3 Weeks

Sub. No.	Screening Wt. (kg)	Period 1 (Weeks 2-4) Bolus	Basal	Total (unit/kg)	Basal/ Total	Period 2 (Weeks 6-8) Bolus	Basal	Total (unit/kg)	Basal/ Total	Avg. Daily Total Insulin Per. 1-2
Semi synthetic - rDNA										
3	76.8	28	19	0.607	0.41	30	18	0.613	0.38	-0.006
4	71.8	16	15	0.436	0.49	28	15	0.603	0.36	-0.168
5	102.7	42	25	0.653	0.39	43	25	0.658	0.40	-0.005
6	84.1	20	17	0.431	0.46	18	17	0.409	0.48	0.002
11	95.0	22	29	0.537	0.57	14	28	0.439	0.67	0.098
12	77.5	31	8	0.502	0.22	32	8	0.515	0.21	-0.013
15	79.1	34	22	0.697	0.40	35	22	0.718	0.39	-0.021
16	76.8	16	18	0.441	0.52	16	16	0.424	0.51	0.017
19	79.5	26	26	0.651	0.50	28	26	0.670	0.48	-0.020
20	81.8	31	40	0.863	0.57	26	40	0.804	0.61	0.059
rDNA - Semi synthetic										
1	85.0	12	19	0.366	0.62	10	19	0.348	0.66	0.018
2	74.7	25	15	0.540	0.39	28	15	0.580	0.35	-0.040
7	101.4	21	22	0.418	0.52	19	22	0.397	0.54	0.021
8	84.5	33	22	0.647	0.41	33	23	0.657	0.41	-0.011
9	97.7	35	19	0.551	0.36	28	17	0.453	0.38	0.099
10	100.0	36	28	0.645	0.45	33	28	0.614	0.46	0.031
13	87.7	31	21	0.589	0.40	29	21	0.568	0.42	0.021
14	84.1	9	25	0.412	0.72	7	19	0.306	0.77	0.105
17	76.4	26	18	0.572	0.42	28	18	0.597	0.40	-0.026
18	86.4	31	50	0.935	0.63	28	51	0.911	0.66	0.024

Data from End-of-text Table 4

There was no difference between the two insulins with respect to change in fructosamine (table 8.2). Given that the average starting value was about 350 umole/L , a mean change of less than 1 umole/L is very small indeed and there was no consistent change among patients.

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Table 8-2: Changes in Fructosamine Levels ~ 350 μ M

Pt. No.	semi synthetic - rDNA P-1	P-2	Change	Pt. No	rDNA - semi synthetic P-1	P-2	Change
3	[redacted]			1	[redacted]		
4				2			
5				7			
6				8			
11				9			
12				10			
15				13			
16				14			
19				17			
20				18			
		Mean	0.34			Mean	0.86
		Median	0.45			Median	0.35
		SD	2.102			SD	2.386

P-1 = Period 1, P-2 = Period 2, Change = Difference between Periods 1 and 2.
Data from End-of-text Table 5.

There was a minor difference between prebreakfast and prelunch glucose values (table 8-4), but these are not of any clinical significance. Semisynthetic insulin gave slightly lower values prebreakfast, but r DNA insulin gave slightly lower values prelunch. It should be borne in mind that these glucose values are finger stick determinations by home glucose monitoring. Thus, the difference in prebreakfast values between 141 mg/dl and 132 mg/dl is probably within the error of the methodology. The fructosamine values were done in a central laboratory and are more reliable.

Table 8-4: Average Pre-Meal and Bedtime Blood Glucose Levels

	rDNA	semi synthetic	Between Treatment Comparison		
No. Treated	20	20	Difference	95% Confidence Interval	p-value*
Blood Glucose (mg/dl)					
Pre-Breakfast					
Mean (SD)	141.2 (28.74)	132.3 (31.27)	-8.9	(-17.1, -0.7)	0.035
Min - Max	97 - 201	86 - 205			
Pre-Lunch					
Mean (SD)	156.5 (38.62)	171.3 (61.20)	14.8	(-0.9, 30.5)	0.063
Min - Max	104 - 234	91 - 312			
Pre-Dinner					
Mean (SD)	140.2 (41.46)	142.9 (32.45)	2.6	(-13.5, 18.8)	0.738
Min - Max	87 - 218	90 - 239			
Bedtime					
Mean (SD)	170.8 (43.53)	175.7 (37.40)	4.9	(-10.7, 20.5)	0.519
Min - Max	88 - 269	97 - 241			

*p-value is ANOVA based on the 2x2 crossover model.
Data from End-of-Text Table 6a

There were no differences between the two treatments in fingerstick glucose values over 400 mg/dl or under 60 mg/dl. There was one major hypoglycemic event on rDNA insulin. All other adverse events were minor and equally distributed between the two treatments.

Recommendation:

The NDA should be approved:

Velosulin (rDNA) is bioequivalent and therapeutically equivalent to Velosulin (semisynthetic).

/S/ [redacted] 12/2/98

Robert I Misbin MD
HFD 510/
NDA 21028/misbin/malozowski/sobel/rheejr
November 20, 1998

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